

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Johannes C. van Groeninghen

Serial No.: 10/327,621

Filed: December 20, 2002

For: METHOD FOR RECOGNIZING AND DETERMINING GNRH RECEPTORS AND USE OF GNRH AGONIST FOR DECREASING THE REPLICATION OF MALIGNANT CELLS BEARING GNRH RECEPTORS OF TUMORS ORIGINATING IN THE NERVOUS SYSTEM AND/OR OF KAPOSI SARCOMA

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((MailingTitle))

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((Mailing4))

((Mailing5))

**DECLARATION OF JOHANNES C. VAN GROENINGHEN, Ph.D.,
UNDER 37 C.F.R. § 1.132**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The undersigned, Dr. Johannes C. van Groeninghen, declare and state:

1. I am an inventor or co-inventor of the invention described in one or more of the claims of U.S. Patent Application 10/327,621, which I am informed and believe is a continuation-in-part of U.S. Patent Application 09/446,996.

2. I am informed and believe that a communication from the United States Patent and Trademark Office was mailed on or about June 23, 2004, regarding the above-referenced application. I am informed and believe that claims 9-24 were rejected under 35 U.S.C. § 112, first paragraph, as assertedly lacking enablement. I am also informed and believe that the communication from the United States Patent and Trademark Office asserted that there is insufficient guidance in the specification of U.S. Patent Application 10/327,621 as to methods using GnRH receptor antagonists to treat oat cell carcinoma, malignant melanoma, or Kaposi's sarcoma.

3. I have reviewed U.S. Patent Application 09/446,996 and U.S. Patent Application 10/327,621.

4. I performed, supervised or directed the experiments that produced the results described herein. The results and data discussed herein indicate that one of ordinary skill in the art would be able to treat *in vivo* oat cell carcinoma, malignant melanoma, and Kaposi's sarcoma using the disclosure as provided in U.S. Patent Application 09/446,996 without undue experimentation. Specifically, U.S. Patent Application 09/446,996 discloses an invention which provides "a medicament for the therapy of," such tumors as those "originating in the brain and/or nervous system and/or the meninges and/or of Kaposi sarcoma," and, more especially, the "use of GnRH agonists and GnRH antagonists and of other ligands of GnRH receptors in the preparation of medicament for the treatment of tumors originating in brain and/or nervous system and/or meninges and/or of Kaposi sarcoma." (See, U.S. Patent Application 09/446,996 at page 5, line 19 to page 6, line 2). U.S. Patent Application 10/327,621, a continuation-in-part of then co-pending U.S. Patent 09/446,996, which incorporated the contents of U.S. Patent 09/446,996 by reference. (See, U.S. Patent 10/327,621 at paragraph [0001]). As is known to one of skill in the art, the oat cell carcinoma is a malignant tumor derived from neural cells. (See, Tecimer, *et al.*, Arch. Pathol. Lab. Med., 124, 520-525, 2000).

5. Using the method as described in the specification on page 39, line [00175], samples of tumors were stained to detect the presence of GnRH receptors on tumor cells. Photographs of stained sections of tumor samples are presented here.

6. Oat cell carcinoma or small cell carcinoma.

Ten metastatic lesions collected from the brain of a patient were analyzed using the method as described on page 39, line [00175] of the specification as filed.

GnRH-receptor staining was detected in said human brain metastasis. A representative example of a stained section is presented in Figure 1. The tumor was classified as an oat-cell carcinoma (syn. small cell carcinoma) metastasis from a primary tumor in the lung. All 10 metastatic lesions were found to be GnRH-receptor positive.

7. Melanoma

Samples were collected from melanoma lesions of 5 patients. The presence of GnRH receptors on the surface of samples of human melanoma or Small Superficial Melanoma (SSM) is shown in the figures 5-8, 10-12, and 14-20./ Positive staining for GnRH receptor is visualized by a pink or orange to yellow staining of the cytoplasm and cell membrane. The negative nuclei are counterstained with a blue color.

Figure 5 represents a sample of a small superficial melanoma from patient no. 2679 showing clear yellow staining of GnRH receptors in scattered cells in tissue and in vessels. Fig 6 represents a sample of a small superficial melanoma from patient no. 3500, showing distinct positive cells (pink). Figure 7 and 8 represent samples of a small superficial melanoma from patient no. 7388. Large GnRH-receptor positive cells are shown in pink to yellow. Figure 10, 11, and 12 represent samples of a small superficial melanoma from patient no. 8541. Many GnRH-receptor positive cells are shown in yellow. Figure 14 to 20 represent samples of a small superficial melanoma from patient no. 9367. GnRH-receptor positive cells are shown in pink to yellow. The tissue samples shown in above-described figures were stained as described on page 39, line [00175] of the specification as filed.

I further enclose a copy of a Research Letter published in the Lancet, Vol. 352, no:9125, August 1, 1998, page 372, entitled: The effects of luteinising-hormone releasing hormone on nervous-system tumours.

I further enclose two papers concerning the *in vivo* inhibiting effect on growth and metastatic activity of melanoma cells:

-A paper by R Moretti et al, J. Clin. Endocrin. & metabolism 87 (8):3791-3797 entitled: Locally expressed LHRH receptors mediate the oncostatic and antimetastatic activity of LHRH agonists on melanoma cells.

-A paper by R Moretti et al, Endocrine-related Cancer (2003) 10, 161-167, entitled: Inhibitory activity of luteinising hormone-releasing hormone on tumor growth and progression.

I further enclose a paper by P. Limonta et al in Frontiers in endocrinology 24 (2003) 279-295 entitled: The biology of gonadotropin hormone-releasing hormone: role in the control of tumor growth and progression in humans. Special reference is being made to the abstract, line 20-22 and to page 286, the bottom half of the right column under the heading 5.2 Hormone-unrelated tumors.

8. Kaposi sarcoma

Samples of cells were collected from Kaposi sarcoma lesions from 3 patients. The presence of GnRH receptors on the surface of samples of Kaposi sarcoma of different patients is presented in figure 2, 3, 4, 9, and 13. Figure 2, 3 and 4 are samples of Kaposi sarcoma collected from patient 12342/02. GnRH positive staining (orange to yellow) was detected in many tumor cells in tissue and in vessels. Figure 9 is from patient 8982/03. GnRH-receptor positive staining (intense yellow) was detected mainly on tumor cells in vessels. Figure 13 is from patient 9012/02. GnRH-receptor positive staining was detected on tumor cells in vessels and on a scattered tumor cells in tissue. The GnRH-receptor positive staining is visualized by an orange to yellow staining of the cytoplasm and cell membrane. The negative nuclei are counterstained with a blue color. The tissue samples shown in above-described figures were stained as described on page 39, line [00175] of the specification as filed.

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9. I hereby declare that all statements are made of my own knowledge, are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both under § 1001 of Title 18 of the United States Code, and that such willful statements may jeopardize the validity of the application or any patent issued therefrom.



Dr. Johannes C. van Groeninghen

October 21, 2004

Date